TAB 12 **Statistics Background Information**

STATISTICAL ISSUES OF STUDY DESIGN AND ANALYSES

The current 1994 Tentative Final Monograph (TFM) for Healthcare Antiseptic Drug Products recommends test methodologies and procedures for the evaluation of three indications: healthcare personnel handwash, preoperative skin preparation and surgical hand scrub. However, there are several statistical issues and limitations of the study designs and the analyses proposed in the document.

This background document summarizes the statistical issues that have been identified as problematic during evaluation of previous and pending NDAs (Section I). In addition, an outline is provided to help clarify data collection procedures and timing for the currently recommended test methods (Section I I). The March 23 NDAC discussion will build on this information. Using blinded data from existing NDAs, potential solutions to the existing issues will be presented for discussion.

I. SUMMARY OF ISSUES:

1) **Active Control** - The current TFM requires a well controlled, randomized, blinded and parallel study for the indications of healthcare personnel hand wash, pre-operative skin preparation and surgical hand scrub. However, the role of an active control is not well defined except that it is used for only internal validation of the test methodology. Ideally, statistical analyses should reflect on the study design and the efficacy analyses should be conducted while borrowing strength of evidence from the active and/or vehicle controls. A superiority or non-inferiority trial may be the possible options. However, due to lack of historical data available on these types of products, it would be difficult to establish non-inferiority margins. In addition, even though vehicle and placebo arms are mentioned in the TFM, majority of the NDAs only include data on active control and test products. The requirement for adequate and well-controlled trials are clearly explained in the CFR.

2) **Sample Size** - In the current TFM, sample size is determined based on historical data using a comparative analysis with a 20% margin on the average log reduction with respect to active control. Currently, the proposed sample sizes are 66 subjects per arm for surgical hand scrub, 96 subjects per arm for pre-operative skin preparation and 54 subjects for healthcare personnel handwash. However, the basis for the sample size calculations is not based on the trial design or the efficacy analyses.

3) **Log Reduction Criteria** - The primary endpoint is the log reduction in bacterial counts from the baseline, which is a surrogate endpoint. Efficacy of the product is demonstrated based on a pre-defined log reduction criterion (example 2-log or 3-log reductions from baseline depending on the test site and sampling time) and the clinical relevance of which, has not been established. Also, there are no data available to justify the threshold log reductions.

4) **Variability** - The primary endpoint of log reductions from baseline may have relatively large variability and the current efficacy criteria is only based on meeting the average log reduction of the active control, without considering the variability of the outcomes. Consequently, a few extreme observations could potentially drive the efficacy results. Use of confidence intervals would provide information about the variability of the outcomes.

II. INDICATIONS AND TESTING CRITERIA

The log reduction criteria, test sites and the sampling times for healthcare personnel handwash, preoperative skin preparation and surgical handscrub are as follows:

Healthcare Personnel Handwash

The effectiveness of the test product for healthcare personnel handwash is evaluated for immediate and persistent antimicrobial activity. The multiple wash procedure is repeated a total of 15 times with at least five minutes between each wash. After the 1st and 10th washes, the hands are sampled.

Table 1: Sampling times for healthcare personnel handwash effectiveness test

	Baseline Period	Immediate (≤ 5 min.)
Day 0	X	
1st Wash at Day 1		X
10th Wash at Day 1		X

According to the log reduction criteria, the test product and the positive control must meet:

- A 2.0 $\log_{10}$ reduction in CFU/cm^2 of an indicator organism (Serratia marcescens) on hand immediately (within 5 minutes) after the 1st wash.
- A 3.0 $\log_{10}$ reduction in CFU/cm^2 of an indicator organism (Serratia marcescens) on hand immediately (within 5 minutes) after the 10th wash.

Preoperative Skin Preparation

There are two test sites (abdomen and groin sites) for this indication, Test subjects are required to have sufficient numbers of resident bacterial flora to permit evaluation of microbial reduction. The so called "study criteria for inclusion" requires subjects to have baseline counts for right and/or left abdomen site to be ≥ 2.2 $\log_{10}$ CFU/cm^2 of skin, and for right and/or left groin site to be ≥ 4.0 $\log_{10}$ CFU/cm^2 of skin.

Treatments of test product, positive control, or vehicle control are randomly assigned to contra-lateral anatomical sites of enrolled subjects, and left and right test sides of each subject are sampled respectively at each sampling point, where a standard randomization or a block randomization is applicable. After scoring the washed area for irritation, a sample is taken from abdomen and groin 10 minutes after the washed area is dry. After these samples have been collected, a sterile bandage will be placed over the washed area to prevent contamination with germs. The subject comes back 6 hours later to have the sample area scored for irritation and sampled.

Table 2: Sampling times for preoperative skin preperation

	Baseline	Immediate	6 hrs.

	Period	(≤ 10 min.)	
Day 0	X		
Abdomen: Day 1		X	X
Groin: Day 1		X	X

Based on the log reduction criteria, the test product and the positive control must meet:

- A 2.0 $\log_{10}$ reduction from baseline in CFU/cm^2 of skin on abdomen site immediately (within 10 minutes) after product use.
- A 3.0 $\log_{10}$ reduction from baseline in CFU/cm^2 of skin on groin site immediately (within 10 minutes) after product use.
- The CFU cell count of skin from both abdomen and groin sites must do not exceed the baseline within 6 hours after product use.

Surgical Hand Scrub

For this indication, subjects are selected from a group of volunteers who have refrained from using any antimicrobials for at least two weeks prior to initiation of the test. Subjects with baseline counts, ≥ 1.5 x 10^6 per hand are selected to enter the treatment phase of the study. A standard randomization or a block randomization is applicable to assign the subjects to test, positive control, or vehicle control group.

One-half of the subjects' hands are sampled immediately after scrubbing (within five minutes) and the remaining hands six hours after scrubbing. No more than one hand of a subject is sampled at a given time interval. Ten additional scrubs are performed with the test formulation over a five-day period following the initial scrub. The hands are sampled two additional times, once after the second scheduled use of the product at Day 2 and again after the last scheduled scrub at Day 5.

Table 3: Sampling times for surgical hand scrub

	Baseline Period	Immediate (≤ 5 min.)	6 hrs.
Day 0	X		
1st Scrubbing at Day 1		X	X
2nd Scrubbing at Day 2		X	
10th Scrubbing at Day 5		X	

Based on the log reduction criteria in the TFM, the test product and the positive control must meet:

- A 1.0 $\log_{10}$ reduction from baseline in CFU/cm^2 of the microbial hand flora immediately (within five minutes) after the 1st scrubbing on Day 1 with the count remaining below baseline 6 hours after scrubbing.

- A 2.0 $\log_{10}$ reduction from baseline at the immediate (within five minutes) sampling after the 2nd scrubbing on Day 2.

- A 3.0 $\log_{10}$ reduction from baseline at the immediate (within five minutes) sampling after the 10th scrubbing on Day 5.